Slide 1

Type 2 Diabetes and Obesity: Pathophysiology, Diagnosis & Treatment Goals

Usah Lilavivat, MD, FACP, FACE, FACN, CDE

March 12, 2011

Myrtle Beach, South Carolina

1

Slide 2

2

Slide 3
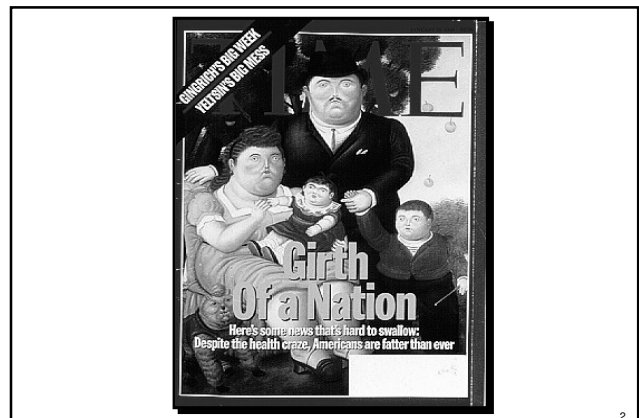
- **FAT PEOPLE CAUSE GLOBAL WARMING:** The rising number of fat people was yesterday blamed for global warming. Scientists warned that the increase in big-eaters means more food production a major cause of CO_2 gas emissions warming the planet. Overweight people are also more likely to drive, adding to environmental damage.

3

Slide 4

One in six United States youths is now overweight.

Mann CC. *Science*. 2005;307(5716):1716-1717.

4

Slide 5

Average Weight (lbs) of 5'8" Men in the United States From 1857-1991

5

Slide 6

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 1999, 2009
(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)

No Data   <10%   10%–14%   15%–19%   20%–24%   25%–29%   ≥30%

6

WHY ARE WE SO fat?

Multi-Hormonal Control of Body Weight: Role Of Fat-, Gut-, and Islet-Derived Signals

Hypothalamus
Vagal afferents
Adipose tissue
Hindbrain
GI tract
Leptin
CCK
Ghrelin
Insulin
PYY$_{3-36}$
Amylin
GLP-1
Visfatin
Resistin
OXM
Adiponectin
GIP
PP
Pancreatic islets

Adapted from Badman MK, et al. *Science.* 2005;307(5717):1909-1914.

8

Energy Homeostasis

Body weight

Increase   Decrease

Energy intake	Energy expenditure
Ingestion of:	Physical activity
Proteins	Diet-induced thermogenesis
Fats	Basal metabolic rate
Carbohydrates	

9

Obesity and Metabolic Syndrome: A Cluster of Coronary Heart Disease Risk Factors

Obesity

Diet Physical Inactivity Stress

Raised Blood Pressure

Genetic Susceptibility

Autonomic Dysfunction

Prothrombotic State
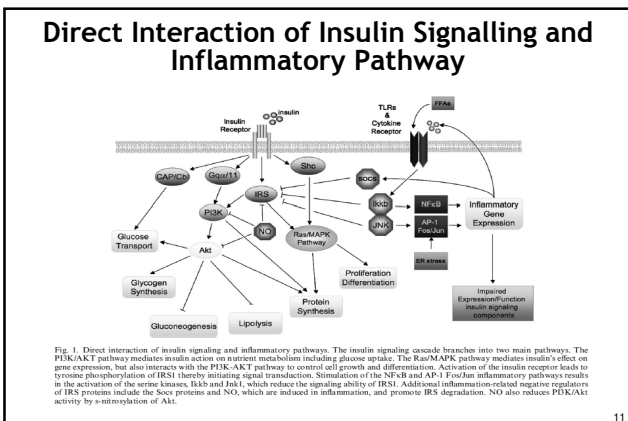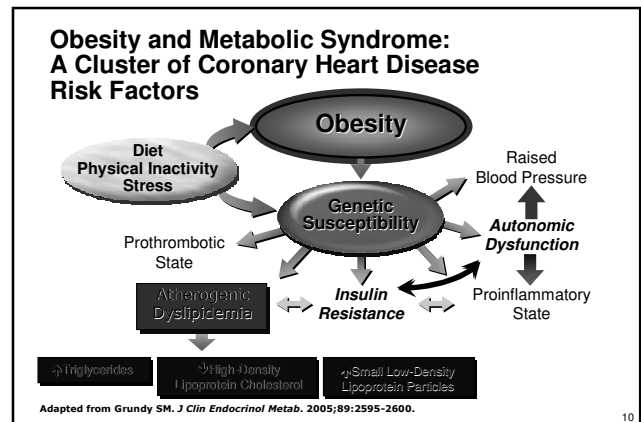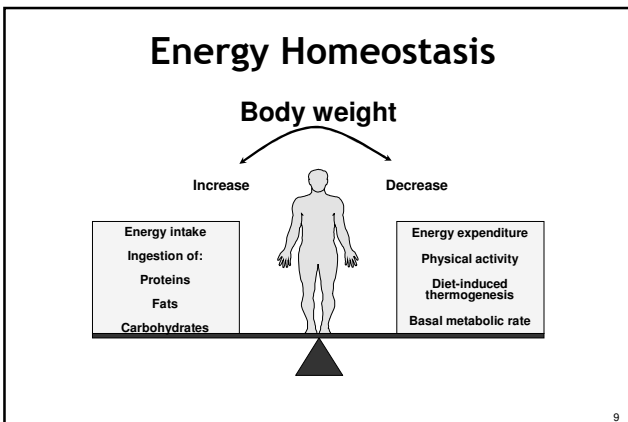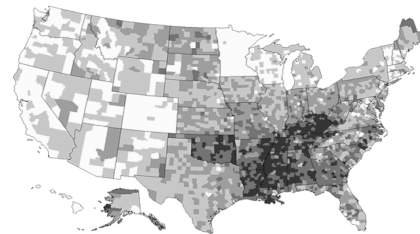
Insulin Resistance

Proinflammatory State

Atherogenic Dyslipidemia

↑Triglycerides   ↓High-Density Lipoprotein Cholesterol   ↑Small Low-Density Lipoprotein Particles

Adapted from Grundy SM. *J Clin Endocrinol Metab.* 2005;89:2595-2600.

10

Direct Interaction of Insulin Signalling and Inflammatory Pathway

Fig. 1. Direct interaction of insulin signaling and inflammatory pathways. The insulin signaling cascade branches into two main pathways. The PI3K/AKT pathway mediates insulin action on nutrient metabolism including glucose uptake. The Ras/MAPK pathway mediates insulin's effect on gene expression, but also interacts with the PI3K-AKT pathway to control cell growth and differentiation. Activation of the insulin receptor leads to tyrosine phosphorylation of IRS1 thereby initiating signal transduction. Stimulation of the NFκB and AP-1 Fos/Jun inflammatory pathways results in the activation of the serine kinases, Ikkb and Jnk1, which reduce the signaling ability of IRS1. Additional inflammation-related negative regulators of IRS proteins include the Socs proteins and NO, which are induced in inflammation, and promote IRS degradation. NO also reduces PI3K/Akt activity by s-nitrosylation of Akt.

11

Physiologic Derangement of Insulin Resistance and Inflammatory Pathway Associated with Metabolic Syndrome

Obesity

Skeletal Muscle
-Increased FFA uptake
-Increased extramyocellular adipose
-Macrophage activation/recruitment
-ER stress

Adipose
-Adipocyte hypertrophy
-Macrophage recruitment
-Macrophage polarity switch
-Increased cytokine production
-Increased lipolysis
-ER stress

Liver
-Increased lipid content
-Steatosis
-Kupffer cell activation/recruitment
-Increased cytokine production
-ER stress

IR   IR   IR

Systemic Insulin Resistance and Inflammation

endocrine crosstalk

12

United States Trends in Caloric Intake: NHANES

kcals / Men / Women

x-axis: 1971-4, 1976-80, 1988-94, 1999-00

Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2004;53(4):80-82.

13

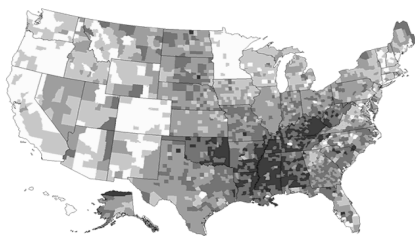## 2004 Age-Adjusted Estimates of the Percentage of Adults Who Are Physically Inactive

Download data: Excel | PPT
Download all maps: PPT
Data Dictionary
Methodology

0 - 19.9
20.0 - 24.1
24.2 - 27.9
28.0 - 32.5
≥ 32.6

14

2008 Age-Adjusted Estimates of the Percentage of Adults Who Are Physically Inactive

Download data: Excel | PPT
Download all maps: PPT
Data Dictionary
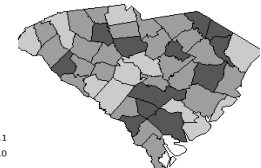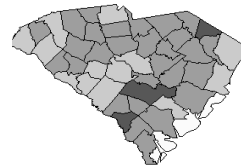Methodology

0 - 19.9
20.0 - 24.1
24.2 - 27.9
28.0 - 32.5
≥ 32.6

15

Age Adjusted Estimated Percentage of Adults Who Are Inactive – South Carolina

2004   2008

≥ 31.2
26.1-31.1
21.1-26.0
0-21.0

16

Former ESA astronaut Claudie Haigneré became the first European woman to fly to the ISS during the Andromède mission in October 2001
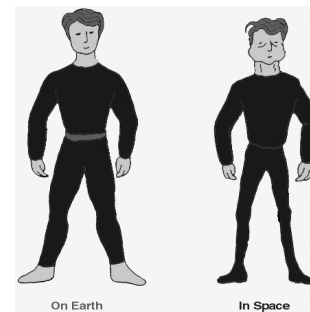
17

Michael Foale is exercising aboard International Space Station

18
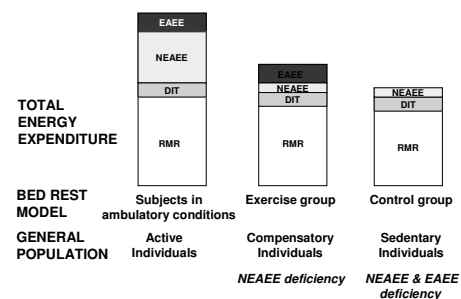
Effect of Weightlessness

On Earth   In Space

Women's International Space Simulation for Exploration (WISE)

Female volunteers are confined to beds that are tilted at -6° from the horizontal from the feet to the head. Every activity, eating, reading, showering etc. is performed in this position for the whole duration of the study at the MEDES Space Clinic in Toulouse, France.

Schematic Representation of the Components of Total Energy Expenditure During Bed Rest, Conducted with or without Exercise Training. EAEE, Exercise Activity Energy Expenditure

TOTAL ENERGY EXPENDITURE			
BED REST MODEL	Subjects in ambulatory conditions	Exercise group	Control group
GENERAL POPULATION	Active Individuals	Compensatory Individuals	Sedentary Individuals
		NEAEE deficiency	*NEAEE & EAEE deficiency*

Bergouignan A et al. *J Clin Endocrinol Metab* 2010;95:1045-1053

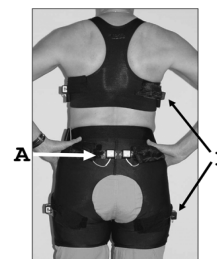## Body Mass and Composition During 60-day Bed Rest Comparing to Ambulatory Baseline
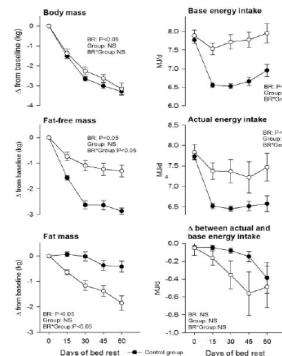
Bergouignan A et al. *J Clin Endocrinol Metab* 2010;95:1045-1053

FIG. 1. *Left panel,* Body mass and composition during the bed rest expressed as changes (kilograms) from ambulatory baseline period in
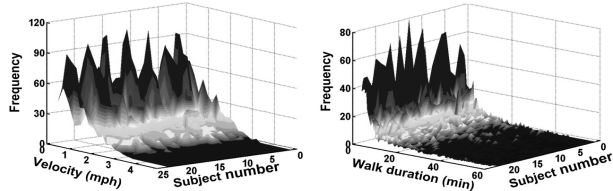
Physical Activity Monitoring System

Levine JA et al. *Diabetes* 2008;57:548-554

Distribution of velocity and duration of walks in free-living people. The distribution of velocity and duration for 10,312 bouts of walking taken by 22 separate subjects (1–22) of varying weight during 10 days of weight-maintenance feeding.
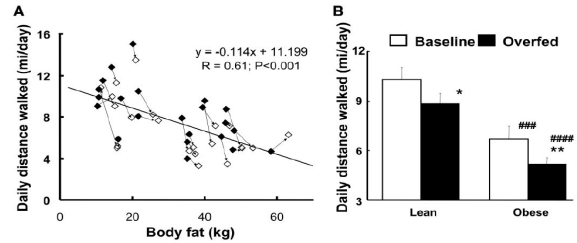

Levine JA et al. *Diabetes* 2008;57:548-554

25

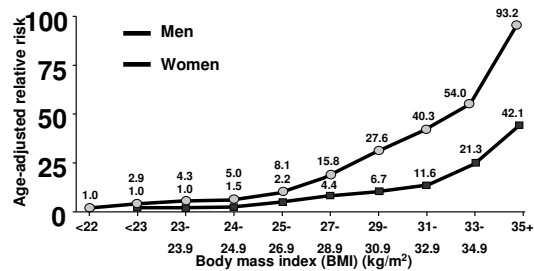**A) Body Fat and Daily Walking Distance in 22 Free-Living People**

B) Daily Walking Distance in Free-Living Lean and Obese Subjects Before and After Overfeeding

A

$y = -0.114x + 11.199$
$R = 0.61; P<0.001$
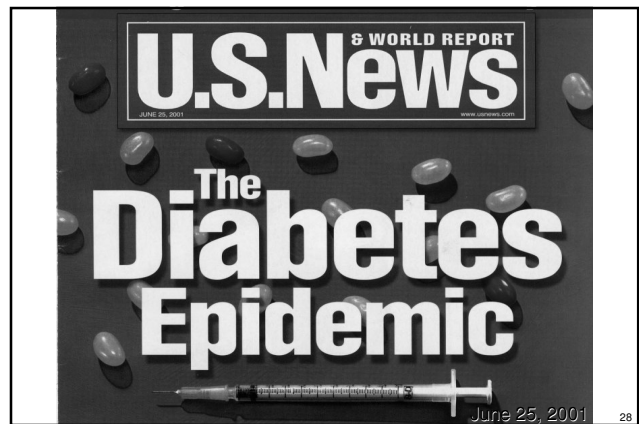
B

Levine JA et al. *Diabetes* 2008;57:548-554

26

Relationship Between BMI and Risk of Type 2 Diabetes

Chan JM, et al. *Diabetes Care*. 1994;17(9):961-969.
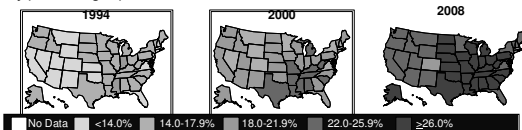Colditz GA, et al. *Ann Intern Med*. 1995;122(7):481-486.

27

June 25, 2001

28

Parallel Epidemics of Diabetes and Obesity

Age-adjusted Percentage of US Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥ 30 kg/m²)

Diabetes
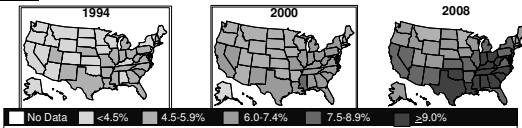
Centers for Disease Control. http://apps.nccd.cdc.gov/ddtstrs/. Accessed March 25, 2010.

29

Prevalence of Type 2 Diabetes Increases with Age

Estimated prevalence of diagnosed and undiagnosed diabetes in people aged 20 years or older, by age group, United States, 2007
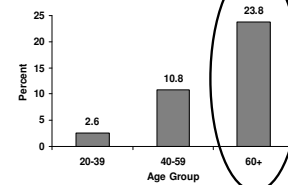
CDC. National Diabetes Fact Sheet, 2007.
Source: 2003–2006 National Health and Nutrition Examination Survey estimates
of total prevalence (both diagnosed and undiagnosed) were projected to year 2007.

30

Slide 31

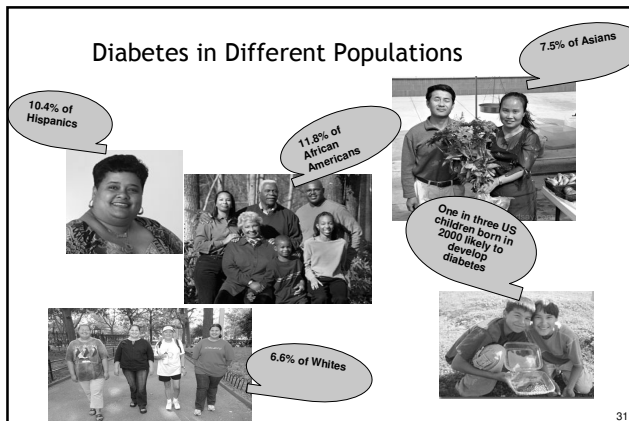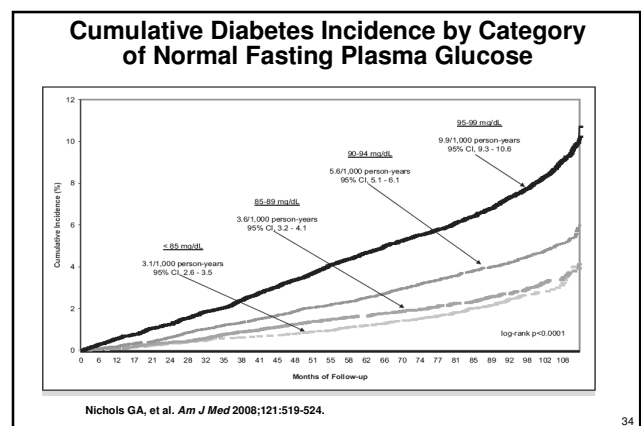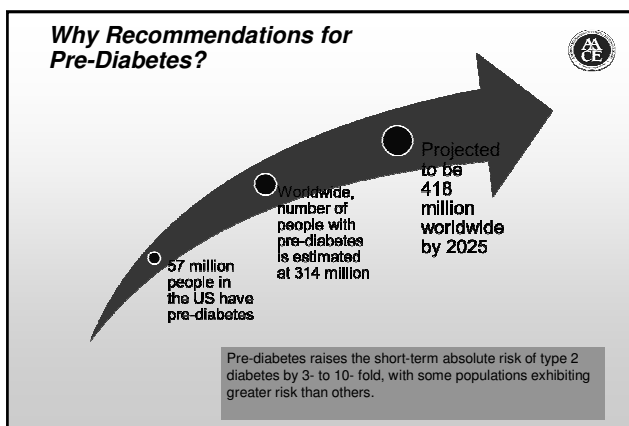### Diabetes in Different Populations

7.5% of Asians

10.4% of Hispanics

11.8% of African Americans

One in three US children born in 2000 likely to develop diabetes

6.6% of Whites

Slide 32

Diagnosis

Pre-Diabetes, Diabetes

Slide 33

Why Recommendations for Pre-Diabetes?

AACE

57 million people in the US have pre-diabetes

Worldwide, number of people with pre-diabetes is estimated at 314 million

Projected to be 418 million worldwide by 2025

Pre-diabetes raises the short-term absolute risk of type 2 diabetes by 3- to 10- fold, with some populations exhibiting greater risk than others.

Slide 34

Cumulative Diabetes Incidence by Category of Normal Fasting Plasma Glucose

95-99 mg/dL
9.9/1,000 person-years
95% CI, 9.3 - 10.6

90-94 mg/dL
5.6/1,000 person-years
95% CI, 5.1 - 6.1

85-89 mg/dL
3.6/1,000 person-years
95% CI, 3.2 - 4.1

< 85 mg/dL
3.1/1,000 person-years
95% CI, 2.6 - 3.5

log-rank p<0.0001

Months of Follow-up

Nichols GA, et al. *Am J Med* 2008;121:519-524.

Slide 35

Measures of Hyperglycemia

- **Random plasma glucose (RPG) —without regard to time of last meal**
- **Fasting plasma glucose (FPG)—before breakfast (8-10 h pc)**
- **Oral glucose tolerance test (OGTT)—2 hours after a 75-g oral glucose drink**
- **Postprandial plasma glucose (PPG)—2 hours after a meal**
- **Hemoglobin A_{1c} (A1c)—reflects mean glucose over 2–3 months**
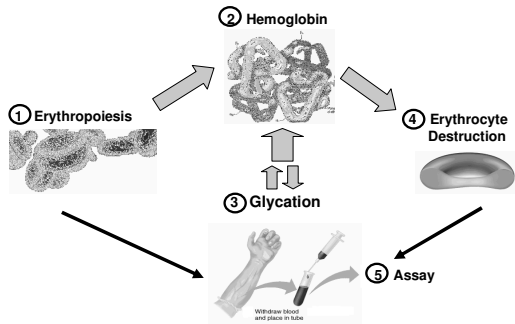- **Fructosamine / glycated serum protein— reflects mean glucose over 1–2 weeks**

Slide 36

2010 Diagnosis of Prediabetes & Diabetes

	Normal	IFG or IGT High Risk for DM	Diabetes*
FPG (mg/dL)	<100	≥ 100 - 125	≥ 126
2-h PG (mg/dL)	<140	≥ 140 - 199	≥ 200
A1c	< 6%	5.7% - 6.4%†	≥ 6.5 %‡

* Random Plasma Glucose ≥ 200 mg/dL + Symptoms

† Require testing FG or GTT; ‡ Confirm with Glucose when possible

Diabetes Care 2010;33 (suppl 1): S11-S61
Endocrine Practice 2010;16:155-156

Factors Influencing A1c

① Erythropoiesis
② Hemoglobin
③ Glycation
④ Erythrocyte Destruction
⑤ Assay

Withdraw blood and place in tube

AACE recommendations:

1. **A1c should be considered an Additional Optional Diagnostic Criterion, not the Primary Criterion for Diagnosis of Diabetes.**

2. **AACE/ACE suggest using traditional Glucose Criteria for Diagnosis of Diabetes when feasible.**

3. **A1c is not recommended for diagnosing Type 1 Diabetes.**

4. **A1c is not recommended for diagnosing Gestational Diabetes.**
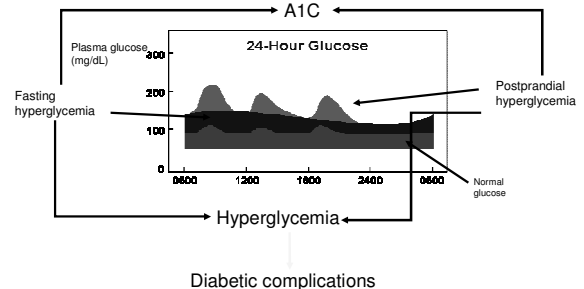
AACE recommendations cont'

5. **A1c may be misleading in several ethnic populations (for example, African American patients).**

6. **A1c may be misleading in the setting of various Hemoglobinopathies, Iron deficiency, Hemolytic anemias, Thalassemias, Spherocytosis, and Severe Hepatic and Renal disease.**

7. **AACE/ACE endorse the use of only standardized, validated assays for A1c testing.**

A1C Reflects Both Fasting and Postprandial Hyperglycemia

A1C

Plasma glucose (mg/dL)

24-Hour Glucose

Fasting hyperglycemia

Postprandial hyperglycemia

Normal glucose

Hyperglycemia

Diabetic complications

A1C = Estimated Average Glucose
A1c (%) to eAG (mg/dl)

6.0% = 126 mg/dl
6.5% = 140 mg/dl
7.0% = 154 mg/dl
7.5% = 169 mg/dl
8.0% = 183 mg/dl
8.5% = 197 mg/dl
9.0% = 212 mg/dl
9.5% = 226 mg/dl
10.0% = 240 mg/dl
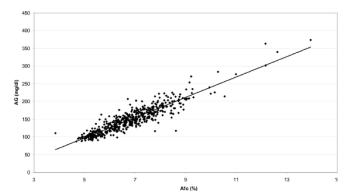
Calculated *eAG mg/dL = 28.7 x A1c – 46.7*
eAG mmol/l = 1.59 x A1c – 2.59

Natham DM et al. *Diabetes Care* 2008;31:1473-1478

Visceral Fat Distribution: Normal vs Type 2 Diabetes

Normal **Type 2 diabetes**
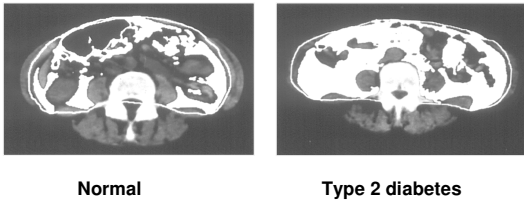
Courtesy of Wilfred Y. Fujimoto, MD.

43

Odds Ratios for the Presence of One or More Obesity-Associated Risk Factors Derived from a Logistic Regression Model for Waist Circumference in Men and Women

— Women — Men

Odds Ratio (y-axis: 0, 2, 4, 6, 8, 10, 12, 14)

Waist Circumference (cm) (x-axis: 66 70 74 78 82 86 90 94 98 102 106 110 114 118)
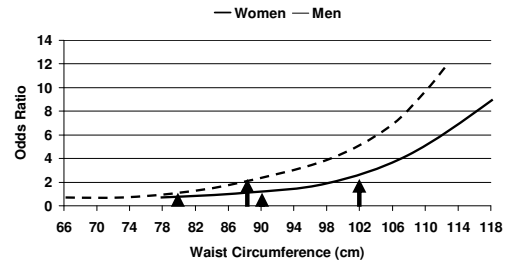
Zhu SK et al *Am J Clin Nutr* 2002;76:743–9

44

Abdominal Obesity: Waist Circumferences in Different Region

	Waist Circumferences (cm) According to Regions		
Gender	North America	Europe	Asia
Male	≥102	≥ 94	≥ 90
Female	≥ 88	≥ 80	≥ 80

45

Clinical Manifestations of Insulin Resistance

Insulin resistance

Glucotoxicity

Lipotoxicity

↓ Adiponectin

Type 2 diabetes and glycemic disorders
Dyslipidemia
– *Low HDL*
– *Small, dense LDL*
– *Hypertriglyceridemia*
Hypertension
Endothelial dysfunction/ inflammation (hsCRP)
Impaired thrombolysis
↑ PAI-1

Atherosclerosis
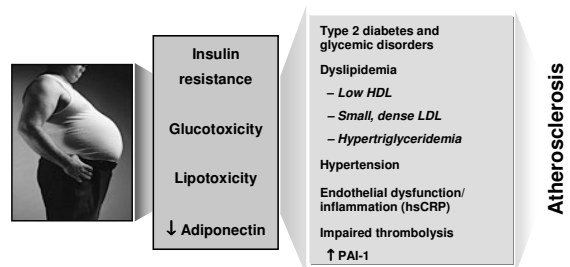
Courtesy of Selwyn AP, Weissman PN.

46

Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion

Genes

Insulin resistance

Lifestyle and diet

Normal β-cell function

Abnormal β-cell function

Hyperinsulinemia

Relative insulin deficiency

Normoglycemia

Hyperglycemia

Type 2 diabetes
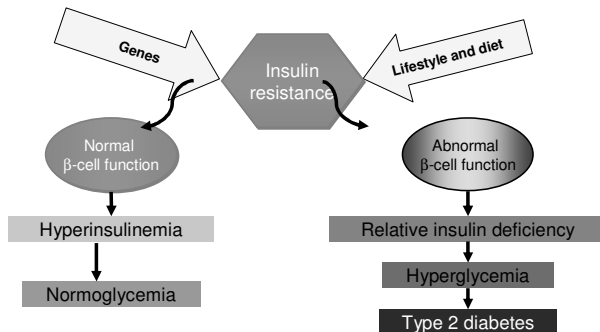
47

Multiple Factors Drive Progressive Decline of β-Cell Function

Hyperglycemia (glucose toxicity)

Insulin resistance

Protein glycation

β-cell

"Lipotoxicity" (elevated FFA, TG)
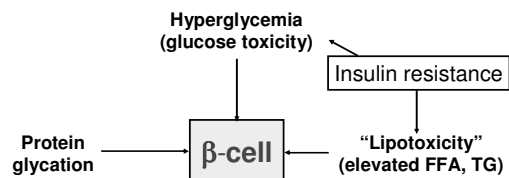
Reaven GM. *Physiol Rev.* 1995;73:473-486.

48

Normal Insulin and Glucagon Response in the Postprandial Period

Carbohydrate meal

Glucose
Insulin
Glucagon

mg/dL — 120, 100, 80
µU/mL — 120, 80, 40, 0
pg/mL — 120, 110, 100, 90

Time (min): −60, 0, 60, 120, 180, 240

Pancreatic islet

α-cells   β-cells

30 MM

Islet boundary

Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science

Unger RH. *N Engl J Med.* 1971;285:443-449.

49

Blood Glucose mg/100 ml   Plasma Insulin µU/100 ml

Obese subjects

- Severe diabetes 2 hrs. blood glucose >300 mg/100 ml
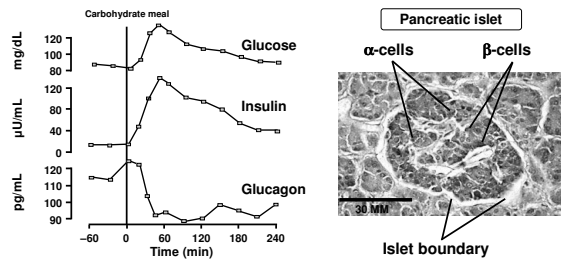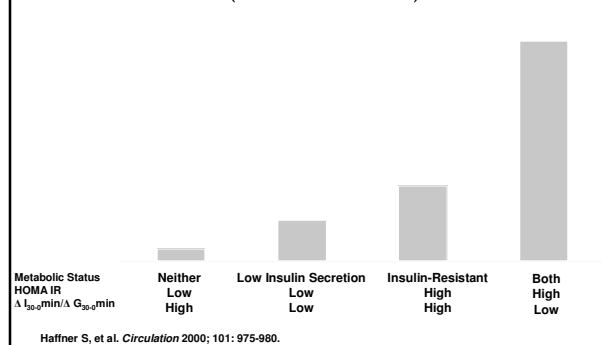- Moderate diabetes
- Nondiabetic

Blood Glucose axis: 400, 300, 200, 100 — (8), (36), (26)
Plasma Insulin axis: 200, 100

Time: 0, 2, 4, 6 hrs.

Yalow, R.S.; Glick, S.M.; Roth, J.; Berson, S.A., *Annals NY Academy Sciences*, 131:357, 1965.
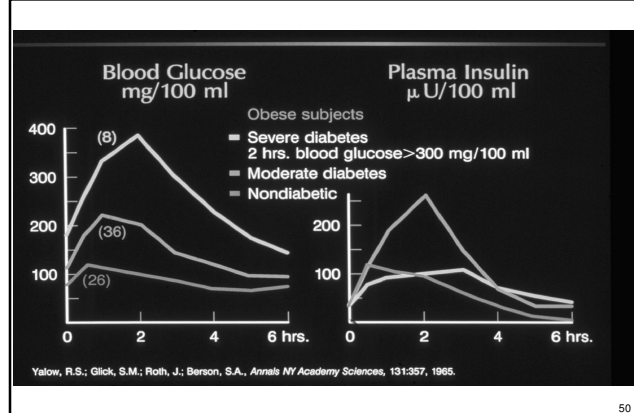
50

Progression Reflects Increasing Imbalance Between Insulin Supply and Demand

Diagnosis

Glucose
— Postprandial glucose
— Fasting glucose

Insulin
— Insulin demand
— Insulin supply

Inadequate β-cell function → Decreasing β-cell function → β-Cell Failure

Microvascular changes →

Macrovascular changes →

NGT | Prediabetes (IGT/IFG) | Diabetes →
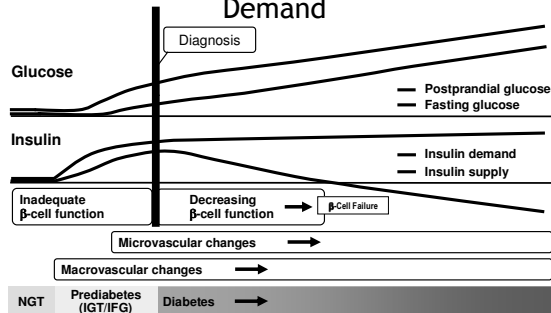
IGT = impaired glucose tolerance; IFG = impaired fasting glucose; NGT = normal glucose tolerance
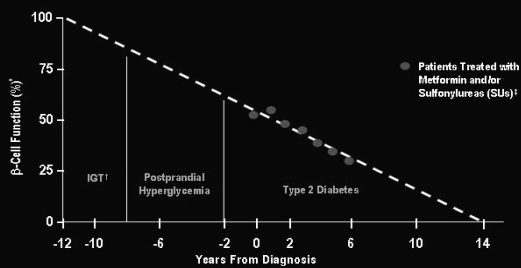Rickheim P, et al. *Type 2 Diabetes BASICS Curriculum Guide.* 2nd ed. 2004.

51
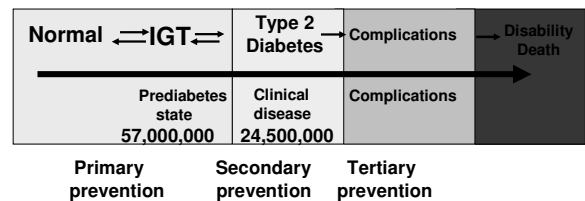

Conversion to Type 2 Diabetes
(7-Year Incidence)

Metabolic Status HOMA IR Δ I$_{30-0}$min/Δ G$_{30-0}$min	Neither Low Low	Low Insulin Secretion Low Low	Insulin-Resistant High High	Both High Low

Haffner S, et al. *Circulation* 2000; 101: 975-980.

52

Can The Decline Be Altered?
UKPDS: β-Cell Decline Over Time

β-Cell Function (%): 100, 75, 50, 25, 0

Patients Treated with Metformin and/or Sulfonylureas (SUs)‡

IGT† | Postprandial Hyperglycemia | Type 2 Diabetes

Years From Diagnosis: -12, -10, -6, -2, 0, 2, 6, 10, 14

*Dashed line shows extrapolation backward from year 0 and forward from year 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS. † IGT = impaired glucose tolerance. ‡ The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model. Adapted with permission from Lebovitz HE. *Diabetes Rev.* 1999;7:139-153. ©1999 American Diabetes Association.

Type 2 Diabetes: A Progressive Disease

Normal ⇌ IGT ⇌	Type 2 Diabetes	Complications	→ Disability Death
Prediabetes state 57,000,000	Clinical disease 24,500,000	Complications	
Primary prevention	**Secondary prevention**	**Tertiary prevention**	

Garber AJ, Handelsman Y, Einhorn D, et al. *Endocr Pract.* 2008;14:933-46.
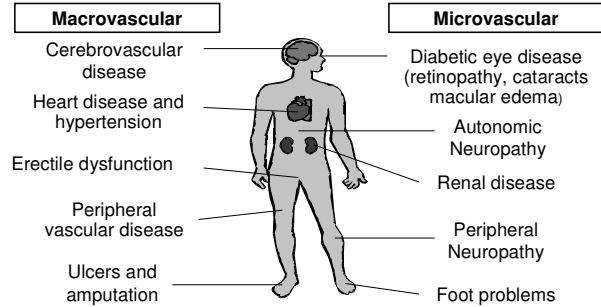
54

Hyperglycemia Damages Tissues

- Effects of hyperglycemia
  - Glycation of proteins (eg, hemoglobin, collagen)
  - Accumulation of sorbitol and fructose (eg, in nerves, lens)
  - Activation of protein kinase C (eg, on vascular cells)
- Tissue changes
  - Altered protein function and turnover, cytokine activation
  - Osmotic and oxidative stress
  - Reduced motor and sensory nerve conduction velocity
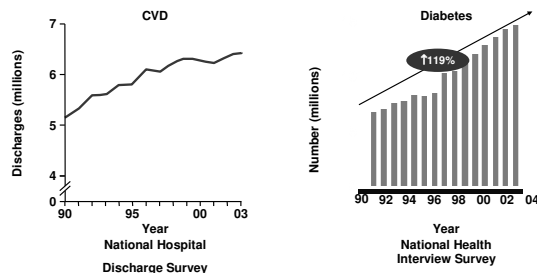 - Increased glomerular filtration rate and renal plasma flow

Aronson D. Adv Cardiol. 2008;45:1-16. Setter SM, et al. Ann Pharmacother. 2003 Dec;37(12):1858-66.
Graf RJ, et al. Ann Intern Med. 1981 Mar;94(3):307-11.

55

Diabetes Complications

Macrovascular		Microvascular

Macrovascular:
- Cerebrovascular disease
- Heart disease and hypertension
- Erectile dysfunction
- Peripheral vascular disease
- Ulcers and amputation

Microvascular:
- Diabetic eye disease (retinopathy, cataracts macular edema)
- Autonomic Neuropathy
- Renal disease
- Peripheral Neuropathy
- Foot problems

CVD Has Risen, Accompanied by Diabetes

CVD — Discharges (millions), Year, National Hospital Discharge Survey

Diabetes — Number (millions), ↑119%, Year, National Health Interview Survey

Thom T, et al. AHA. *Circulation.* 2006;113(6):e85-e151.

Centers for Disease Control. http://www.cdc.gov/nchs/nhis.htm. Accessed March 25, 2010.

57

Prevalence of Diabetes Macrovascular and Microvascular Complications

Macrovascular   Microvascular
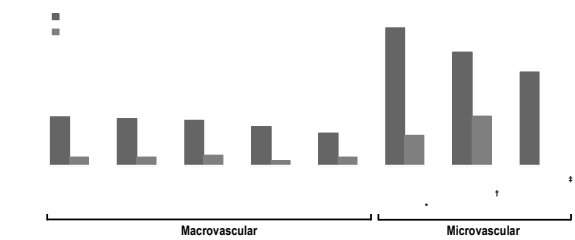
*In NHANES, "chronic kidney disease" refers to people with microalbuminuria (albumin:creatinine ratio >30 µg/mg).
†In the NHANES analysis, "foot problems" includes foot/toe amputations, foot lesions, and numbness in the feet.
‡"Eye damage" includes a positive response by NHANES participants to the question, "Have you been told diabetes has affected your eyes/had retinopathy?" Retinopathy is damage to the eye's retina. In NHANES, people without diagnosed diabetes were not asked this question, therefore, prevalence information for nondiabetics is not available.

American Association of Clinical Endocrinologists. State of Diabetes Complications in America Report. Available at:
http://www.aace.com/newsroom/press/2007/images/DiabetesComplicationsReport_FINAL.pdf. Accessed April 18, 2007.

58

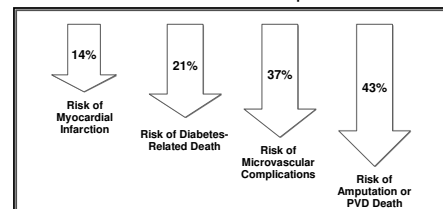## Risk of Complications in Type 2 Diabetes

Any End Point Related to Diabetes*

Hazard Ratio

P<.0001

HbA_{1c}

21% risk decrease per 1% decrement in HbA_{1c}
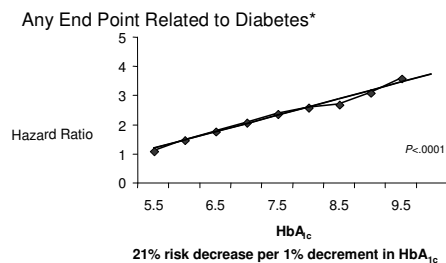
*Reference category (hazard ratio 1.0) is HbA_{1c} <6% with log linear scales. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density LDL and triglycerides.
Adapted from Stratton IM, et al. (UKPDS 35). *BMJ.* 2000;321:405-412.

59

Benefits of Glycemic Control

Every 1% decrease in A1C leads to significant reductions in complications

- 14% Risk of Myocardial Infarction
- 21% Risk of Diabetes-Related Death
- 37% Risk of Microvascular Complications
- 43% Risk of Amputation or PVD Death

Decrease was statistically significant for all comparisons shown.

Results are from an epidemiologic analysis (Stratton IM et al. *BMJ.* 2000;321:405-412).
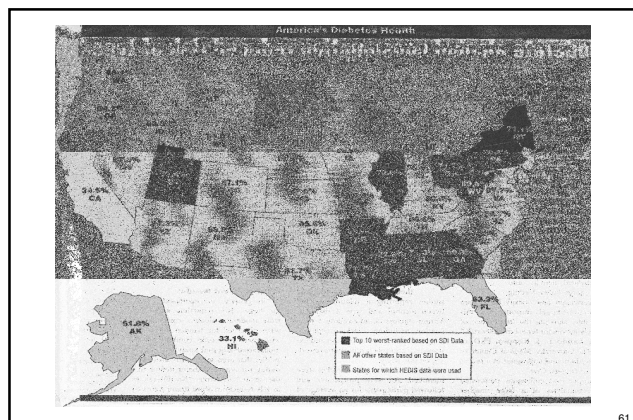
61

Diabetes Treatment Goals

	AACE	ADA
•HgA1c	<6.5	<7 (to "normal"<6 safely)
•Fasting BG/pre meal	<110	90-130
•Postprandial	<140**	<180*
•Blood pressure	<130/80	<130/80
•LDL Cholesterol	<100 (**<70***)**	<100
•HDL Cholesterol	>40	>40
•Triglyceride	<150	<150
•Aspirin/Plavix		
•ACE/ARB		
•Beta Blockers		

-*Peak
-**2 hours postmeal
-***Lower goals recommended for
-high risk CVD

Standard of Care – _Team Work_

Diet	**Education**	**Exercise**	**SMBG**
Microalbumin/e-GFR		**Eyes**	**Feet**

Diabetic symmetric polyneuropathy
Autonomic Neuropathy Cardio vascular disease

ADA. Standards of Medical Care in Diabetes 2010. Diabetes Care. 2010 Jan 1;

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. _Endocr Pract._ 2007;13:(suppl 1)3–68.

62

Weight Change and Mortality in Diabetes

Intentional loss resulted in a relative risk reduction† of:
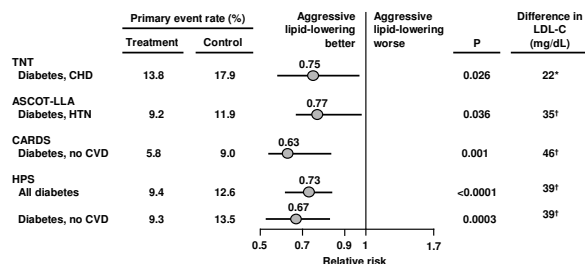- 22% ↓ all-cause death
- 24% ↓ death from CVD + diabetes
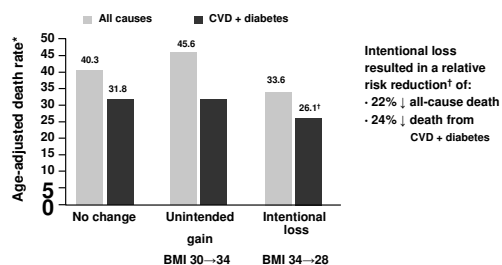
*Mortality rates are directly age-standardized to the age distribution of the cohort and expressed per 1000 person-years.
†Adjusted for age, sex, initial BMI.
Williamson DF, et al. _Diabetes Care._ 2000;23(10):1499-1504. Copyright © 2000 American Diabetes Association.

63

Benefits of aggressive LDL-C lowering in diabetes

*Atorvastatin 10 vs 80 mg/day
†Statin vs placebo

Shepherd J et al. _Diabetes Care_ 2006. Sever PS et al. _Diabetes Care_ 2005. HPS Collaborative Group. _Lancet_ 2003. Colhoun HM et al. _Lancet_ 2004.

64

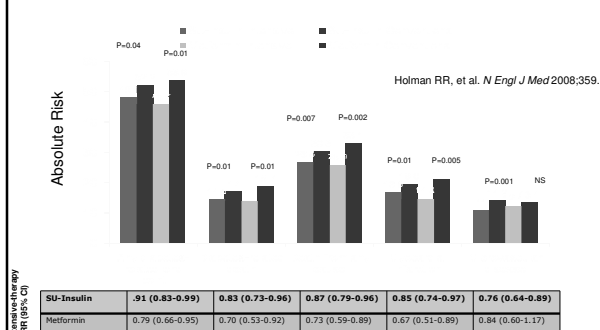## UKPDS: Blood Pressure Control in Type 2 DM
Effect of Intensive BP Lowering on Risk of Micro- & Macrovascular Complications

Benefits of 144/82 vs 154/87
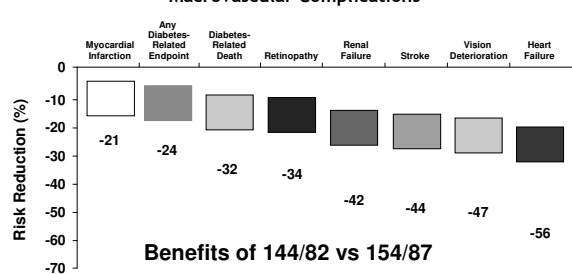
UKPDS Group. UKPDS 38. _BMJ._ 1998;317:703-713.

65

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Holman RR, et al. _N Engl J Med_ 2008;359.

SU-Insulin	.91 (0.83-0.99)	0.83 (0.73-0.96)	0.87 (0.79-0.96)	0.85 (0.74-0.97)	0.76 (0.64-0.89)
Metformin	0.79 (0.66-0.95)	0.70 (0.53-0.92)	0.73 (0.59-0.89)	0.67 (0.51-0.89)	0.84 (0.60-1.17)

66

Steno-2: % Reaching Goals

160 Type 2 DM Subjects With Microalbuminuria

Legend: Intensive Rx, Conventional Rx

Percent (y-axis: 0–80)

Categories: HbA$_{1C}$ <6.5% | TC <175 mg/dL | TG <150 mg/dL | SBP <130 mm Hg | DBP <80 mm Hg
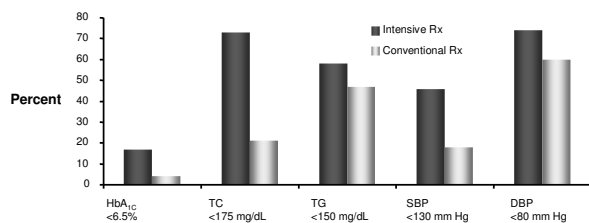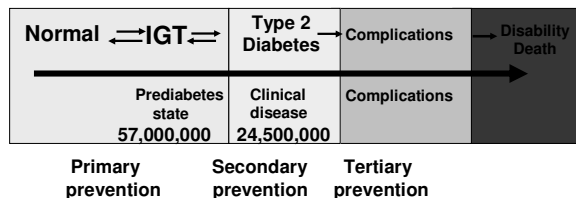
Gaede P et al. *N Engl J Med.* 2003;348:383-393.

67

Summary- Diabetes Complications

- The Obesity epidemic leads to Diabetes & CVD epidemic
- Utilize Lifestyle modification for prevention & treatment
- Institute Intensive treatment for glycemic control
- Benefits of Statins and LDL-lowering in diabetic patients
- Benefit of ACE/ARB in HTN in Diabetes
- Consider comprehensive care of all risk factors, with combination medications, to reduce CVD & complication
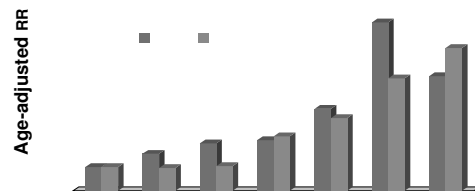
68

Type 2 Diabetes: A Progressive Disease

Normal ⇌ IGT ⇌	Type 2 Diabetes →	Complications	→ Disability Death
	Prediabetes state 57,000,000	Clinical disease 24,500,000	Complications

Primary prevention	Secondary prevention	Tertiary prevention

Garber AJ, Handelsman Y, Einhorn D, et al. *Endocr Pract.* 2008;14:933-46.

69

A1C and Coronary Risk in the EPIC Study

Age-adjusted RR

P<0.001 for linear trend across A1C categories for all endpoints.
Data from Khaw KT, et al. *Ann Int Med.* 2004;141(6):413-420.

70

Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis

- **The following increase the risk of developing diabetes associated with normal fasting plasma glucose**
  - Obesity
  - Hypertension
  - Low HDL cholesterol
  - High triglycerides
  - Smoking
- **Closer surveillance for diabetes development might be warranted in these patients**

Nichols GA, et al. *Am J Med* 2008;121:519-524.

71

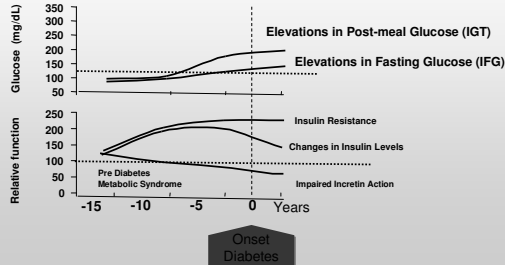**The Diagnosis and Management of Pre-Diabetes in the Continuum of Hyperglycemia—**

When Do the Risks of Diabetes Begin?

American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) CONSENSUS STATEMENT

Progression to Type 2 Diabetes

Glucose (mg/dL): 350, 300, 250, 200, 150, 100, 50

- Elevations in Post-meal Glucose (IGT)
- Elevations in Fasting Glucose (IFG)

Relative function: 250, 200, 150, 100, 50, 0

- Insulin Resistance
- Changes in Insulin Levels
- Pre Diabetes Metabolic Syndrome
- Impaired Incretin Action

-15 -10 -5 0 Years

Onset Diabetes

Defining Interventional Criteria for Pre-Diabetes

1. Impaired fasting plasma glucose levels (IFG at levels of 100-125 mg/dL; 5.5-6.9 mmol/L).
2. Impaired glucose tolerance of 140-199 mg/dL (7.7-11 mmol/L)
   - Patients with impaired glucose metabolism who were discovered by 2-hour OGTT were greater in number than patients discovered by routine determination of fasting glucose alone.
   - In patients with IFG, a 2 hr GTT may further clarify the level of risk while also detecting undiagnosed diabetes.
3. Metabolic syndrome diagnosed by the NCEP criteria should be considered a pre-diabetes equivalent.
   - It predicts future diabetes better than IFG.
   - 3 of 5 criteria of the metabolic syndrome are sufficient; recent evidence suggests even 2 of 5 metabolic syndrome criteria may be adequate as well.
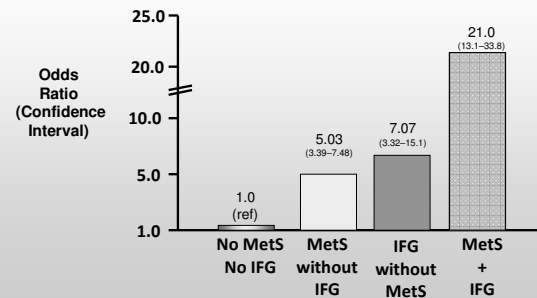

Metabolic Syndrome: NCEP ATP III Criteria (Any 3 of 5)

Risk Factor	Defining Level
✓ Abdominal Obesity	
Men	Waist >102 cm or 40 in. (M)
Women	Waist >88 cm or 35 in. (F)
✓ Triglycerides	≥150 mg/dl
✓ HDL Cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
✓ Blood Pressure	≥130/85 mm Hg*
✓ Fasting Glucose	≥110 mg/dl

* ≥130/80 mm Hg per ADA guidelines *Diabetes Care.* 2002;25: S33-S49
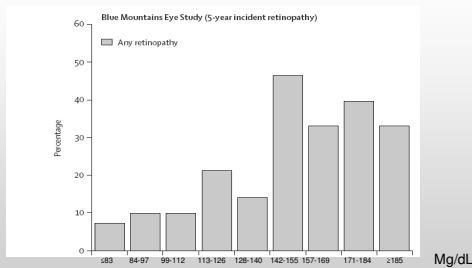NCEP ATPIII *JAMA.* 2001; 285: 2486-2497

75

How Much Does the Metabolic Syndrome Raise the Risk for Diabetes?

Odds Ratio (Confidence Interval)

- No MetS No IFG: 1.0 (ref)
- MetS without IFG: 5.03 (3.39–7.48)
- IFG without MetS: 7.07 (3.32–15.1)
- MetS + IFG: 21.0 (13.1–33.8)

Lorenzo C, et al. *Diabetes Care.* 2007;30:8-13

Relationship Between Fasting Plasma Glucose and 5-Year Incident Retinopathy

Blue Mountains Eye Study (5-year incident retinopathy)
Any retinopathy

Percentage (0–60)

Mg/dL: ≤83, 84-97, 99-112, 113-126, 128-140, 142-155, 157-169, 171-184, ≥185

Wong TY, et al. *Lancet* 2008; 371: 736–43.

Impaired Glucose Tolerance and Peripheral Neuropathy

- Diabetes is the most common cause of peripheral neuropathy
- Up to 1/3 of neuropathy patients have no identifiable etiology
  - Among this population, IGT is observed in approximately 40% of patients, suggesting that neuropathy may occur as a result of pre-diabetes
- Treatment of IGT patients with diet and exercise reduces the risk of progression to diabetes and those with neuropathy experience a short-term improvement in small fiber function, with sustained benefit for pain

Singleton AG & Smith JR. *Neurologist* 2008;14:23-29.

Slide 1

Slide 2
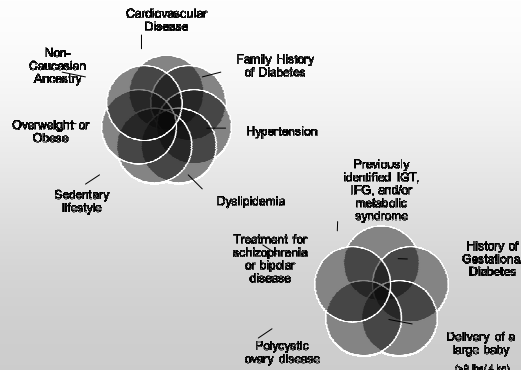
Criteria for Testing for Diabetes in Asymptomatic Adult Individuals

1. Testing should be considered in all adults who are overweight (BMI 25 kg/m^2*) and have additional risk factors:

- Physical Inactivity
- First-Degree Relative with Diabetes
- High-Risk Race/Ethnicity (i.e. AfA, Lto, Nat A, AA, Pac Isd)
- Woman w Baby BW >9 lbs or Hx of GDM
- Hypertension (BP ≥140/90 mmHg or on Rx for HTN)
- HDL < 35 mg/dl (0.90 mmol/l) and/or Trig >250 mg/dl (2.82 mmol/l)
- Women w PCOS
- A1c ≥5.7%, IGT, or IFG on Previous Testing
- Other Clinical Setting Associated w Insulin Resistance (Severe Obesity, Acanthosis nigricans)
- History of CVA

*At-risk BMI may be lower in some ethnic groups

80

Slide 3

Criteria for Testing for Diabetes in Asymptomatic Adult Individuals (cont')

2. In the absence of the above criteria, testing for diabetes should begin at age 45 years.

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

- To test for diabetes or to assess risk of future diabetes, A1C, FPG, or 2-h 75-g OGTT is appropriate.
- In those identified with increased risk for future diabetes, identify and, if appropriate, treat other CVD risk factors.

ADA Position Statement – Standards of Medical Care in Diabetes – 2011
Diabetes Care 2011;34(suppl 1):S11-S61

81

Slide 4

Testing for Type 2 Diabetes in Asymptomatic Children

Criteria

- Overweight (BMI 85th percentile for age and sex, weight for height 85th percentile, or weight 120% of ideal for height)

Plus Two of the Following Risk Factors

- Family history of type 2 diabetes in firstor second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-forgestational-age birth weight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

ADA Position Statement: Standards of Medical Care in Diabetes – 2011
Diabetes Care 2011;34(suppl 1):S11-S61

82

Slide 5

Testing by		Results		
Impaired fasting glucose	<100 mg/dL (<5.5 mol/L)	100-125 mg/dL (5.5-6.9 mmol/L)	≥125 mg/dL (7 mmol/L)
Impaired glucose tolerance	< 140 mg/dL (<7.7 mmol/L)	140-200 mg/dL (7.8-11 mmol/L)	≥ 200 mg/dL (≥11 mmol/L)
Indicates:	Normal	Pre-Diabetes	Diabetes

Metabolic syndrome should be considered a pre-diabetes equivalent (3 of 5 criteria)

Slide 6

Sensitivities and Specificities for the Diagnostic Criteria for Diabetes Based on Retinopathy – NHANES 2005-2006

Test	Cut Point	Sensitivities	Specificities
A1c	5.5%	80%	37%
	6.0%	55%	79%
	6.5%	38%	92%
FPG	5.8 mmol/l 104 mg/dl	58%	64%
	6.5 mmol/l 117 mg/dl	43%	84%
	7.0 mmol/l 126 mg/dl	35%	89%
	7.5 mmol/l 135 mg/dl	30%	92%

Cheng YJ et al. *Diabetes Care* 2009;32:2027-2032

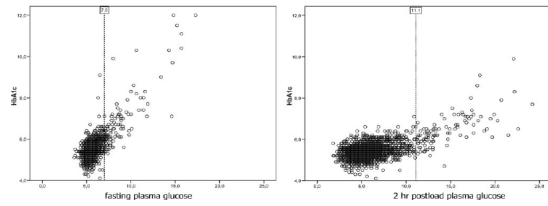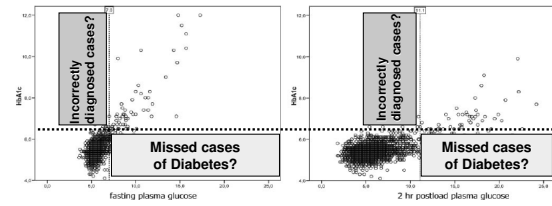84

Diagnostic Criteria for Diabetes: A1c 6.5%?

Figure 1—Scatter plots of FPG and 2-h postload plasma glucose in relation to A1C in the total population. Diabetic patients are indicated by dotted reference lines at FPG levels of 7.0 mmol/l and 2-h postload plasma glucose levels of 11.1 mmol/l.

Hoorn Study: Van'T Riet E et al. *Diabetes Care* 2010;33:61-66

85

Diagnostic Criteria for Diabetes: A1c 6.5%?

Figure 1—Scatter plots of FPG and 2-h postload plasma glucose in relation to A1C in the total population. Diabetic patients are indicated by dotted reference lines at FPG levels of 7.0 mmol/l and 2-h postload plasma glucose levels of 11.1 mmol/l.

Hoorn Study: Van'T Riet E et al. *Diabetes Care* 2010;33:61-66

86

Feasibility of Preventing Type 2 Diabetes

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors:
  – Obesity
  – Body fat distribution
  – Physical inactivity
  – High blood glucose

Type 2 Diabetes Mellitus Prevention: Outcomes of Randomized, Controlled Clinical Trials

Study	Intervention	RRR
DaQing Study[1]	Therapeutic lifestyle change	31-46%
Xenos[2]	Orlistat	37%
Finnish Diabetes Prevention Study[3]	Therapeutic lifestyle change	58%
Diabetes Prevention Program[4]	Therapeutic lifestyle change	58%
Diabetes Prevention Program[4]	Metformin	31%
STOP-NIDDM[5]	Acarbose	25%
TRIPOD[6]	Troglitazone	55%
DREAM[7]	Rosiglitazone	62%

88

Two-Track Approach to Reduce Risk

(1) Lower glucose to prevent microvascular complications and progression to diabetes
- Lifestyle Intervention
- Pharmacotherapy in high risk patients

(2) Address cardiovascular disease risk factors
- Lifestyle Intervention
- Blood pressure goals: <130/80 mm Hg
- LDL goal: <100 mg/dL

Interventions to Reduce the Risks Associated with Pre-Diabetes

- Intensive lifestyle management is the cornerstone of all prevention efforts
- No pharmacologic agents are currently approved for the management of pre-diabetes.
  – Pharmacotherapy targeted at glucose may be considered in high risk patients after individual risk: benefit analysis.

Pre-Diabetes Consensus Statement: Summary

- **Untreated individuals with pre-diabetes are at increased risk for diabetes as well as for micro- and macro-vascular complications**
- **Treatment goals are to prevent deterioration in glucose levels and modify other risk factors, such as obesity, hypertension, and dyslipidemia**
  - The same BP and lipid goals for pre-diabetes as for diabetes are suggested
- **Intensive lifestyle management is the cornerstone of all prevention efforts, pharmacotherapy targeted at glucose may be considered in high risk patients after individual risk:benefit analysis**

ADA Recommendation for Treating IFG, IGT, or Both

Recommendation	Treatment
Population: IFG, IGT, or A1c 5.7 – 6.4%	Lifestyle modification (i.e. 7% weight loss and moderate-intensity physical activity of 150 min/wk) Fiber 14 g/1000 kcal, whole grain – ½ of grain intake.
• Follow-up counseling important for success • Based on potential cost savings, such programs should be covered by third party payors ∗ *Monitor all for development of DM annually*	• Consider Metformin in those at higher risk for DM, multiple risk factors, w progression of A1c ≥6% **∗**
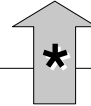
Technology Progress and the Diabesity Epidemic